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ONE HUNDRED NINTH CONGRESS

# Congress of the United States

## House of Representatives

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## MEMORANDUM

May 5, 2005

**To:** Democratic Members of the Government Reform Committee

**From:** Rep. Henry A. Waxman

**Re:** The Marketing of Vioxx to Physicians

On November 9, 2004, the Committee on Government Reform requested that Merck provide the Committee with a wide range of documents related to the anti-inflammatory drug Vioxx. The request expressly sought “all presentations, training sessions, or materials given to Merck employees and agents who marketed Vioxx” and “all records of communication provided to healthcare providers and pharmacists concerning the safety and efficacy of the drug.”<sup>1</sup> In response to this request, Merck provided the Committee with over 20,000 pages of internal company documents, including course curricula, bulletins to the field, training manuals, company talking points, memoranda among senior executives, and promotional materials for use with physicians. The Committee also received documents from FDA related to Vioxx.

These documents provide an extraordinary window into how Merck trained its sales representatives and used them to communicate to physicians about Vioxx and its health risks. In fact, the documents may offer the most extensive account ever provided to Congress of a drug company’s efforts to use its sales force to market to physicians and overcome health concerns.

To assist members in their preparation for the May 5, 2005, hearing on FDA and Vioxx, this memorandum summarizes the key documents received by the Committee. It assesses how Merck trained its sales representatives, whether this training was consistent with a primarily educational purpose for contacts with physicians, and whether Merck’s sales representatives were instructed to discuss fairly and accurately the cardiovascular risks of Vioxx with physicians.

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<sup>1</sup> Letter from Chairman Tom Davis to Merck Chief Executive Officer Ray Gilmartin (Nov. 9, 2004).

The Committee did not receive documents from Pfizer related to its anti-inflammatory drugs Celebrex and Bextra, nor has the Committee received or reviewed documents from other drugs companies related to the marketing of other drugs. Thus, this memorandum cannot assess whether Merck’s practices are better or worse than or the same as those of other drug companies.

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## EXECUTIVE SUMMARY

By the time Merck voluntarily withdrew the anti-inflammatory drug Vioxx from the market in September 2004, more than 100 million prescriptions had been dispensed in the United States. Yet the vast majority of these prescriptions were written by physicians after evidence of Vioxx's risks had already surfaced. Even as evidence mounted that use of Vioxx was associated with heart attacks and strokes, physicians continued to prescribe Vioxx to millions of patients. How could this have happened?

A partial answer may be found by examining the strategies that Merck used to market Vioxx to physicians. Based on a review of the Merck documents, it appears that Merck sent over 3,000 highly trained representatives into doctor's offices and hospitals armed with misleading information about Vioxx's health risks. The documents indicate that Merck instructed these representatives to show physicians a pamphlet indicating that Vioxx might be 8 to 11 times safer than other anti-inflammatory drugs, prohibited the representatives from discussing contrary studies (including those financed by Merck) that showed increased risks from Vioxx, and launched special marketing programs — named "Project XXceleration" and "Project Offense" — to overcome the cardiovascular "obstacle" to increased sales.

The documents reveal that Merck exhaustively trained its representatives on how to persuade doctors to prescribe Vioxx and other Merck products. No interaction with physicians appears to have been too insignificant for instruction. Merck representatives were taught how long to shake physicians' hands (three seconds), how to eat their bread when dining with physicians ("one small bitesize piece at a time"), and how to use "verbal and non-verbal" cues when addressing a physician to "subconsciously raise[] his/her level of trust." Merck instructed its representatives on the various personality types of doctors (including "technical," "supportive," and "expressive") and recommended targeted sales techniques for each type. And Merck rewarded its sales force with thousands of dollars in cash bonuses for meeting sales goals. The company assigned individual doctors a "Merck potential" and graded them on how often they prescribed Merck products.

The documents describe in detail how Merck used this highly trained sales force to respond to reports of Vioxx's safety risks. The first public indication that Vioxx posed a heightened risk of heart attack and stroke came in March 2000, when Merck's VIGOR study showed a five-fold increase in the risks of heart attacks in patients on Vioxx compared to patients on naproxen. This study was followed by cautionary discussions of the cardiovascular risks of Vioxx at a meeting of an advisory committee to the Food and Drug Administration in February 2001, in a *New York Times* article in May 2001, and in a paper in the *Journal of the American Medical Association* in August 2001.

After each of these developments, Merck sent bulletins or special messages to its sales force, directing them to use highly questionable information to assuage any physician concerns.

For example, the Merck documents show:

- **After Merck’s VIGOR study reported increased heart attack risks, Merck directed its sales force to show physicians a “Cardiovascular Card” that made it appear that Vioxx could be 8 to 11 times safer than other anti-inflammatory drugs.** This card omitted any reference to the VIGOR findings and was based on data FDA considered to be inappropriate for a safety analysis.
- **After the FDA advisory committee voted that physicians should be informed about the risks found in the VIGOR study, Merck sent a bulletin to its sales force that advised: “DO NOT INITIATE DISCUSSIONS ON THE FDA ARTHRITIS COMMITTEE ... OR THE RESULTS OF THE ... VIGOR STUDY.”** If physicians asked about the VIGOR study, Merck representatives were directed to respond, “I cannot discuss the study with you.”
- **After the *New York Times* reported on the cardiovascular dangers of Vioxx, Merck instructed its field staff to tell physicians that patients on other anti-inflammatory medications were eight times more likely to die from cardiovascular causes than patients on Vioxx.** The Merck bulletin told its sales force to show physicians the Cardiovascular Card and state: “Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was Vioxx .1 vs. NSAIDS .8 vs. Placebo 0.”

After extensive negotiations, FDA and Merck agreed on a label change for Vioxx in April 2002 that mentioned the cardiovascular findings from the VIGOR study. The final label included the statement that the significance of these findings were “unknown.” According to the documents, Merck instructed its representatives to emphasize this statement on new label to counter physician safety concerns.

Drug companies maintain publicly that their representatives play a vital role in the health care system by educating physicians about new drugs and ongoing research. But the Merck documents reveal another side to company marketing efforts. The documents show that Merck trained its representatives to capitalize subtly on every interaction with physicians to promote Merck products. When concerns about Vioxx’s safety arose, Merck appeared to use this highly trained force to present a misleading picture to physicians about the drug’s cardiovascular risks. Merck’s promotional efforts appear to explain in part why Vioxx sales remained strong even as the evidence of the drug’s dangers mounted.

## I. INTRODUCTION

On September 30, 2004, Merck & Co, Inc., announced that in a major clinical trial, patients on the anti-inflammatory drug Vioxx had experienced significantly more heart attacks and strokes than those on a placebo. On the same day, Merck voluntarily withdrew Vioxx from the market.<sup>2</sup>

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<sup>2</sup> Merck, *Merck Announces Voluntary Worldwide Withdrawal of Vioxx* (Sept. 30, 2004) (online at [http://www.vioxx.com/vioxx/documents/english/hcp\\_notification\\_physicians.pdf](http://www.vioxx.com/vioxx/documents/english/hcp_notification_physicians.pdf)).

At the time of Vioxx's withdrawal, more than 2 million patients around the world were taking the drug.<sup>3</sup> Since May 1999, when Vioxx was approved by the Food and Drug Administration, more than 100 million prescriptions had been dispensed in the United States alone.<sup>4</sup> Vioxx is considered safer for the stomach than aspirin and other anti-inflammatory drugs. Yet recent research indicates many, if not most, patients on Vioxx were at low or very low risk of stomach problems and would have done well on standard medications.<sup>5</sup>

When exposure to a drug is so widespread, even a small safety problem can have major public health consequences. A recent study estimated that as many as 88,000 to 140,000 Americans may have suffered Vioxx-related heart attacks, strokes, and other serious medical complications.<sup>6</sup>

The vast majority of Vioxx prescriptions were written after serious safety questions were first raised. In March 2000, less than a year after approval, Merck announced the results of a clinical trial in which Vioxx was associated with significantly more heart attacks and strokes than another anti-inflammatory drug.<sup>7</sup> Paradoxically, following the announcement of these results, Vioxx's sales soared. The drug reached \$2 billion in sales faster than any other drug in Merck's history.<sup>8</sup>

Vioxx sales remained strong even as other reports of Vioxx's dangers emerged. These included new data presented at an FDA advisory committee in February 2001,<sup>9</sup> a major exposé in the *New York Times* in May 2001,<sup>10</sup> an article in the *Journal of the American Medical*

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<sup>3</sup> *Merck: Vioxx Withdrawal a Harsh Blow to Drug Giant*, Chicago Tribune (Oct. 3, 2004).

<sup>4</sup> D. Graham et al., *Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclo-oxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Nested Case-Control Study*, *Lancet*, 475–481 (Feb. 5, 2005).

<sup>5</sup> Carolanne Dai, Randall S. Stafford, G. Caleb Alexander, *National Trends in Cyclooxygenase-2 Inhibitor Use Since Market Release*, *Archives of Internal Medicine*, 171-177 (Jan. 24, 2005).

<sup>6</sup> *Id.*

<sup>7</sup> *Merck Informs Investigators of Preliminary Results of Gastrointestinal Outcomes Study with VIOXX(R)*, PR Newswire (Mar. 27, 2000).

<sup>8</sup> Merck, *Merck Annual Report 2001, We're Strengthening Our Arthritis Franchise* (2002) (online at <http://www.anrpt2001.com/4.htm>).

<sup>9</sup> Food and Drug Administration, *Arthritis Advisory Committee* (Feb. 8, 2001) (online at <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2.htm>).

<sup>10</sup> *Doubts Are Raised on the Safety of Two Popular Arthritis Drugs*, *New York Times* (May 22, 2001).

*Association* in August 2001,<sup>11</sup> and changes to the Vioxx label in April 2002.<sup>12</sup> Despite growing concern over Vioxx's dangers, sales in 2003 reached \$2.5 billion.<sup>13</sup>

This memorandum summarizes key Merck documents that shed light on why clinicians continued to prescribe so much Vioxx even as evidence of harm began to mount. Based on a review of over 20,000 pages of internal company documents, it focuses on an aspect of the drug industry that has historically been hidden from public view: promotional activities directed at physicians.<sup>14</sup>

Promotions targeting physicians account for the majority of drug industry spending on marketing and promotion. In 2003, pharmaceutical companies spent \$9 billion on marketing and promotion. Of this amount, \$5.7 billion (over 60%) was aimed at physicians.<sup>15</sup> As many as ninety thousand sales representatives meet with physicians about their companies' products every day.<sup>16</sup>

Vioxx was no exception. According to Merck, the company assigned over 3,000 company representatives across the country to engage in face-to-face discussions with physicians about Vioxx.<sup>17</sup>

According to the Pharmaceutical Research and Manufacturers Association of America, an industry trade group, the efforts of pharmaceutical representatives are "essential for

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<sup>11</sup> D. Mukherjee, S. Nissen, and E. Topol, *Risk of Cardiovascular Events Associated with Selective Cox-2 Inhibitors*, *Journal of the American Medical Association*, 954–9 (Aug. 22–29, 2001).

<sup>12</sup> Food and Drug Administration, *FDA Approves New Indication and Label Changes for the Arthritis Drug, Vioxx*, FDA Talk Paper (Apr. 11, 2002).

<sup>13</sup> *Merck Withdraws Arthritis Medication*, *Washington Post* (Oct. 1, 2004).

<sup>14</sup> Other factors beyond the scope of this report have been cited as contributors to robust Vioxx sales. These include Merck's \$300 million direct-to-consumer advertising campaign and FDA's failure to strongly and promptly warn the public and physicians of cardiovascular risks. *See New Study Criticizes Painkiller Marketing*, *Washington Post* (Jan. 25, 2005); Daniel H. Solomon, Jerry Avorn, *Coxibs, Science, and the Public Trust*, *Archives of Internal Medicine*, 158-160 (Jan. 24, 2005);

<sup>15</sup> According to the Pharmaceutical Research and Manufacturers Association, drug companies spent \$5.7 billion on office promotion, hospital promotion, and journal advertising in 2003, compared to \$3.3 billion in direct-to consumer advertising. They also spent an additional \$16.3 billion in providing samples of medications to physicians. PhRMA, *Pharmaceutical Research and Promotion* (Nov. 2004).

<sup>16</sup> *It's All in the Detail*, *Med Ad News* (Oct. 1, 2004).

<sup>17</sup> Teleconference briefing by Merck for staff of the Government Reform Committee (Apr. 25, 2005).

physicians, allowing physicians to have sufficient information about new drugs so they can prescribe them appropriately.”<sup>18</sup> The trade group also has stated, “Many physicians learn about new drugs — indeed, about ongoing research in their areas of specialization — largely through information provided by the companies that market new products.”<sup>19</sup>

In fact, the documents suggest that Merck’s sales representatives did not appropriately educate physicians about the research showing Vioxx’s cardiovascular risks. To the contrary, it appears that Merck’s highly trained sales force was instructed not to address the new research findings, but to emphasize outdated and misleading data that indicated Vioxx was safer than alternatives. The documents thus raise serious questions about the role played by Merck’s representatives in physician prescribing of a risky drug.

## **II. HOW MERCK TRAINED ITS SALES REPRESENTATIVES**

The documents reveal that the 3,000-person sales force Merck used to promote Vioxx to physicians was extraordinarily well trained. Virtually every possible interaction with physicians — from the act of shaking hands to navigating through complex hospital power struggles — is addressed in some portion of the Merck materials. The overriding goal of the training appears clear: to maximize sales of Merck products.

This part of the memorandum describes the general training Merck provided to its sales representatives. This training instructed the representatives in techniques thought to enhance “professional presence” and “captivate the customer.” It also addressed sensitive subjects such as medical reprints, physician targeting, hospital dynamics, and physician education. Although not addressed here, Merck representatives were also required to attend numerous courses and exercises covering a variety of medical topics, including pharmacology, anesthesiology, rheumatology, and pain management.<sup>20</sup>

The next part of this memorandum (part III) examines how Merck used this highly trained sales force to communicate with physicians about the risks of Vioxx.

### **A. General Sales Techniques**

Merck provided its representatives with extensive training in sales techniques. This training emphasized that “gaining access and building relationships ... are key to providing you

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<sup>18</sup> PhRMA, *Marketing and Promotion of Pharmaceuticals* (Oct. 23, 2000) (online at <http://www.phrma.org/publications/quickfacts/23.10.2000.184.cfm>).

<sup>19</sup> *Id.*

<sup>20</sup> *See, e.g., Merck, Analgesic and Anti-Inflammatory Training, Modules 1-8* (undated).

the opportunity to influence your customers' behaviors."<sup>21</sup> Merck's sales staff were instructed that a successful career can depend upon "how you present yourself professionally."<sup>22</sup>

Some of the training materials addressed the basic elements of a visit with physicians. For example, the course *Selling Skills* instructed representatives to begin by "painting a word picture that describes a patient type that can benefit from the Merck product." *Selling Skills* then advised that representatives ask "strategic questions" about the physician's approach to the patient that "help you influence and control the discussion," which should be followed by a transition to a "compelling message" for the Merck product. The fourth step in the process involved "obstacle handling," which addresses overcoming physician concerns about the product. Finally, *Selling Skills* instructed representatives that the last step of a visit is "closing," which involves summarizing "the point(s) you want the customer to remember," checking for agreement, asking for "a specific, realistic, measurable action," and "follow-up to ensure action."<sup>23</sup>

Other training materials taught more sophisticated and subtle techniques. For example, one Merck course, entitled "Access Success," advised representatives to master nonverbal cues to communicate effectively with doctors.<sup>24</sup> See Figure 1.

**Figure 1: Merck Instruction on Face-to-Face Communication**

<b>Verbal (7%)</b> <i>What someone says when listening. . .</i>	<b>Vocal (38%)</b> <i>How they say something when listening. . .</i>	<b>Visual (55%)</b> <i>What they're doing when listening. . .</i>
<ul style="list-style-type: none"> <li>▪ Hmm, Yes, Okay, I see</li> <li>▪ Acknowledge</li> <li>▪ Ask questions</li> <li>▪ Summarize</li> <li>▪ Stay open to ideas</li> <li>▪ Short periods of silence</li> </ul>	<ul style="list-style-type: none"> <li>▪ Sound interested</li> <li>▪ Mimic or match vocal behavior of speaker</li> <li>▪ Use voice inflection and energy</li> <li>▪ Use empathetic voice</li> </ul>	<ul style="list-style-type: none"> <li>▪ Nod head</li> <li>▪ Eye contact</li> <li>▪ Smile (if appropriate)</li> <li>▪ Don't interrupt</li> <li>▪ Take notes</li> <li>▪ Openness in gestures</li> </ul>

<sup>21</sup> Merck, *Professional Presence* (undated).

<sup>22</sup> *Id.*

<sup>23</sup> Merck, *Selling Skills for Hospital Representatives & HIV Specialists* (undated).

<sup>24</sup> Merck, *Access Success* (Apr. 2000).

Similarly, the course “Captivating the Customer” recommended that field staff learn nonverbal techniques involving the eyes, head, fingers and hands, legs, overall posture, facial expression, and mirroring.<sup>25</sup> Curriculum notes for leaders of the course explained the last concept further:

Mirroring is the matching of patterns; verbal and non-verbal, with the intention of helping you enter the customer’s world. It’s positioning yourself to match the person talking. It subconsciously raises his/her level of trust by building a bridge of similarity.<sup>26</sup>

In a course entitled “Champion Selling,” Merck sought to teach staff to “employ a variety of selling skills and techniques to more effectively handle challenging selling situations.”<sup>27</sup> One such technique was to analogize the “defining moments” of selling Merck drugs to critical points in the lives of “champions” in other fields, including Helen Keller, Martin Luther King, Tiger Woods, and even George Washington.<sup>28</sup> See Sidebar.

Another important technique emphasized in “Champion Selling” was to assess the personality of doctors in order to determine what type of information would be most convincing to them. For a doctor with a “technical” personality, sales representatives were taught to “use figures, percentages” in their pitches; for a doctor with a “supportive personality,” representatives were advised to “focus on benefits to patients”; and for a doctor with an “expressive personality,” representatives were told to “show enthusiasm; appeal to his/her ego.”<sup>29</sup>

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<sup>25</sup> Merck, *Captivating the Consumer* (June 2001).

<sup>26</sup> *Id.*

<sup>27</sup> Merck, *Champion Selling: Milestone Leader’s Guide* (Jan. 2002).

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

### **Sidebar: Analogies in Champion Selling**

*Champion Selling* instructed that when faced with a doctor who does not have time to talk about a Merck product, field staff should recall that “it’s those defining moments that distinguish all champions.” Course leaders were asked to remind trainees:

- Helen Keller could have felt sorry for herself when she went blind and deaf.
- Martin Luther King could have laid low when his home was firebombed.
- Tiger Woods could have avoided the pressure by not turning pro as young as he did.
- George Washington could have finished his years with a comfortable life without the challenges of taking on the presidency.\*

\* Merck, *Champion Selling: Milestone Leader’s Guide* (Jan. 2002).

Merck paid special attention to teaching its field representatives how to “refocus a conversation from non-business subjects to business subjects.”<sup>30</sup> In one curriculum, sales representatives were asked to judge sample responses to statements from doctors such as “What a nice restaurant! I hear that the food is wonderful,” “I love coming to this restaurant, my husband I come here a lot,” “What a great football game yesterday,” and “So what plans do you have for the holidays?”<sup>31</sup> One response suggested for discussion to the last question was:

Well, my wife and I are going to visit my grandmother. It should be a lot of fun though I feel so bad for her. She really has advanced osteoporosis and can’t travel at all. She wasn’t on any treatment plan for the longest time. Physician, what do you think the reasons are that some physicians don’t do much about osteoporosis until it’s in its advanced stages and nearly too late?<sup>32</sup>

Another curriculum instructed representatives to use a “respond → advance” model to move conversation gradually from general topics to selling Merck products.<sup>33</sup> See Figure 2.

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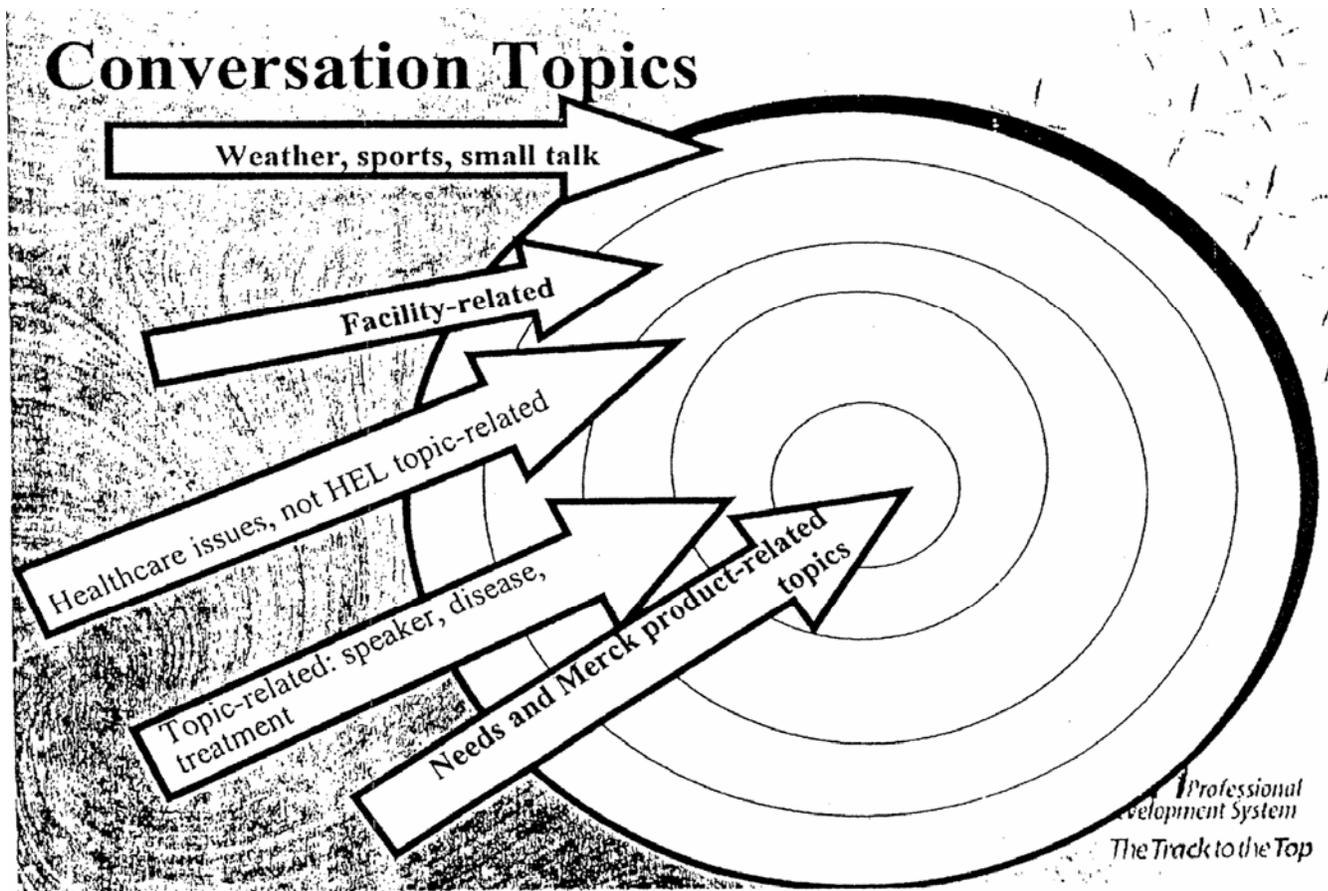
<sup>30</sup> Merck, *Planning, Conducting & Following up Successful HEL Programs* (1999).

<sup>31</sup> *Id.*

<sup>32</sup> *Id.*

<sup>33</sup> Merck, *Ensuring Rewarding HEL Programs* (Apr. 2000).

Figure 2: Instructions on Transitioning Topics

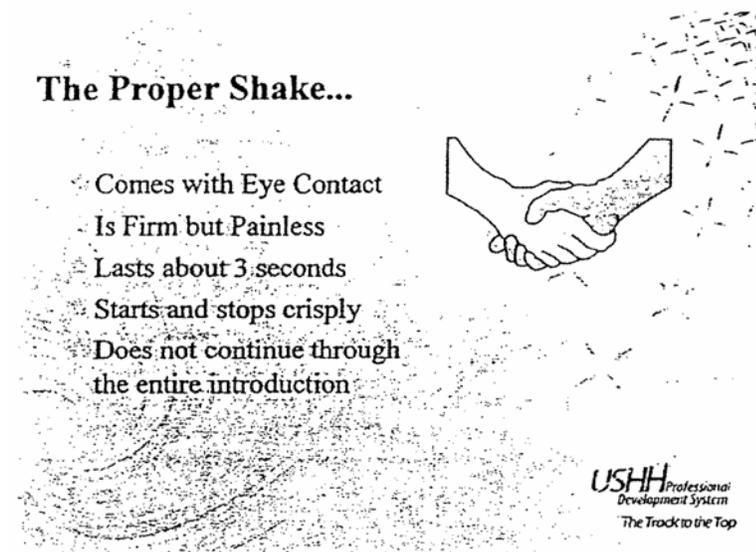


The documents show that Merck trained its sales staff on minute details of encounters with physicians. One Merck training course, entitled “Professional Presence,” even provided detailed instructions on handshakes.<sup>34</sup> See Figure 3. The curriculum advised representatives to shake hands when “someone offers his/her hand to you,” when “first meeting someone,” when “greeting guests,” when “greeting your host/hostess,” when “renewing an acquaintance,” and when “saying good-bye.”<sup>35</sup>

<sup>34</sup> Merck, *Professional Presence* (undated).

<sup>35</sup> *Id.*

**Figure 3: Merck Instruction on Handshake Technique**



Another section of the same course instructed representatives on where to sit and how to eat when dining with physicians. For example, the curriculum stated: “Bread should be eaten one small bitesize piece at a time. Break off and butter bread one single piece at a time. Bread dipped in olive oil should also be broken off and eaten one single piece at a time.”<sup>36</sup>

## **B. Specific Marketing Strategies**

In addition to training its staff in general sales techniques, the documents show that Merck provided its sales representatives with detailed instructions on a range of sensitive subjects specific to the marketing of drugs. The subjects covered in these materials included selectively using reprints from the medical literature that supported Merck products, tracking detailed prescribing behavior of each clinician in their territory, modeling how to get Merck drugs on hospital formularies, and fostering contact between representatives and key opinion leaders.

**Medical Reprints.** Merck representatives were trained to use reprints of medical journal articles in sales discussions, but only when those articles presented Merck products in a favorable light. One course workbook instructed participants that medical journal articles relating to Merck drugs fell into two categories: “approved” and “background.” “Approved” articles were those to be discussed with doctors because they “provide solid evidence as to why [doctors] should prescribe Merck products for their appropriate patients.”<sup>37</sup> In contrast, “background” articles were not approved for use with physicians.<sup>38</sup> According to the workbook,

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<sup>36</sup> *Id.*

<sup>37</sup> Merck, *Join the Club* (Mar. 2001).

<sup>38</sup> *Id.*

“These articles may contain valuable background information, but this information cannot be used, and the articles cannot be referenced, during sales discussions with your customers.”<sup>39</sup> In fact, discussing unapproved background articles with physicians “is a clear violation of Company Policy.”<sup>40</sup> Merck instructed representatives to refer any questions about these articles to the medical services department.<sup>41</sup>

**Physician Prescribing Patterns.** The documents reveal that Merck provided its representatives with highly detailed information on individual doctors’ prescribing habits and that this data was used to target physicians to increase their prescribing of Merck drugs. Merck purchased this prescribing data from an outside company, which obtained the data from pharmacy records of filled prescriptions.<sup>42</sup> Based on this data, representatives would be given access to monthly reports on each doctor in their territory. For each doctor, the reports showed the number of filled prescriptions for Merck and competitor products. They also showed each doctor’s “market share” by calculating the percentage of Merck versus competitor product prescriptions. An important concept was each doctor’s “Merck potential,” which Merck defined as a “dollar estimate of each prescriber’s total prescribing volume that can realistically be converted to Merck prescriptions.”<sup>43</sup>

Based on the data for individual doctors, Merck’s software could compile monthly reports on overall sales and market share for each representative’s territory. Representatives were told that their bonuses would be based on these overall sales figures, and representatives could see estimates of their bonus along with the data.<sup>44</sup> Thus, representatives could see a direct correlation between the number of prescriptions they convinced doctors to write each month and their bonuses.

Merck also told the sales representatives that doctors would be given grades from D to A+ for each product category depending on how often they prescribed a Merck product and what percentage of their prescriptions were for the Merck product.<sup>45</sup> See Figure 4.

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<sup>39</sup> *Id.*

<sup>40</sup> *Id.*

<sup>41</sup> *Id.*

<sup>42</sup> Merck, *Data Sources* (May 2003).

<sup>43</sup> Merck, *Basic Training Participant Guide* (Jan. 2002).

<sup>44</sup> *Id.*; Merck, *Foundations Reference Guide, Business Management Field Sales Performance Report* (undated).

<sup>45</sup> Merck, *Basic Training Participant Guide* (Jan. 2002); Merck, *Role of the National Account Executive* (undated).

Figure 4: Example of Merck Tracking of Physician Prescribing

## Physician Profile

### ★ Specialty: Internal Medicine

Cash: 12%

MediCaid: 10%

Mail Order: 10%

3rd Party: 68%

#1 Top Regional Plan: 35% (24% of total market)

# 2 Top Regional Plan: 25% (17% of total market)

Lipids: A, Z Flat (5%), L Inc.(22%), P Dec(34%)

AHTN: B, Coz Dec(23% All) ACEIs 1st, CCBs 2nd., Dioy Flat(50% All)

Migraine: B, Max Inc(10%) Imitrex Dec(80%),

A&A: A-, V Flat (7.6) Ibup Flat(33%), Gel Flat(8.4%),

Osteo: A, FOS flat(59%), ERT 1st, Act Inc(5%), Evi Flat(19%)

Asthma: B, Sing Inc(8%) Acc dec(9%), Flo inc(28%), Ser inc(20%)

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**Hospital Formularies.** Other instruction provided by Merck addressed approaches for getting Merck drugs onto hospital formularies, which are the lists of the drugs easiest for local physicians to access. These strategies included an elaborate simulation in which representatives played an entire cast of hospital staff, including departments of pharmacy, orthopedic surgery, emergency medicine, rheumatology, endocrinology, a pain clinic, internal medicine, anesthesiology, cardiology, nursing, and oncology. The simulation instructions described the “power structures that existed in each department.”<sup>46</sup>

Interactions with hospital staff in the simulation were designed to reveal lessons for representatives such as “the importance of leaving no stone unturned and the fact that all personnel in the hospital are potentially useful to you.”<sup>47</sup> The simulation also showed how doctors’ ambitions could be used to gain formulary support. In one scenario, a doctor described as an “ambitious Attending Physician” wants “sponsorship to enable him to attend a major symposium in Sydney, Australia. . . . He was willing to act as a sponsor for Vioxx if you offered

<sup>46</sup> Merck, *Hospital Strategy Simulation: Roleplayers Guide* (Sept. 2000).

<sup>47</sup> *Id.*

to help him attend the meeting.”<sup>48</sup> In another scenario the fact that two doctors play golf together is used to gain a sponsor.<sup>49</sup>

Departmental power structures were explored in a scene where a senior trauma nurse is “seen by many as running the department” and does not get along with a new “ambitious young Attending Physician.”<sup>50</sup> The nurse sees the young doctor as “rocking the boat,” while he does not like “the power she wield[s],” so the representative in the simulation must turn to a more senior doctor who gets along with the nurse rather than asking the new young doctor for formulary support.<sup>51</sup> In general, the representatives in the simulation learn to gauge who is influential, ambitious, or a potential informer in a given department and to use this knowledge to maximum benefit in the campaign to achieve formulary status.

**Physician Education.** Merck’s extensive training also addressed how sales representatives could use speaker programs and other educational events as opportunities to enhance sales of Merck products. These speaker programs, sometimes referred to as Health Education Learning (HEL) programs, often take the form of a dinner and featured speaker or panel of speakers on a topic of medical interest. Merck advised its representatives to invite speakers based in part on whether they viewed Merck products favorably and whether they were influential among their peers.<sup>52</sup> One curriculum ranked potential speakers as follows:

A preferred speaker is a qualified advocate who is willing and able to conduct multiple HEL programs. Preferred speakers should have outstanding delivery and provide favorable yet balanced HEL presentations. . . . A recommended speaker is a qualified advocate who is willing and able to conduct multiple HEL programs. Recommended speakers also deliver favorable, scientifically balanced programs, however they may not be as strong of a speaker, or as willing to do talks. . . . A speaker classified as “Other” . . . could be one of your speakers in-development, who can deliver favorable, scientifically balanced HEL programs.<sup>53</sup>

In a training for specialty representatives, Merck explained how to create an “Advocate Action Plan” that would help them “sell through the science, by combining scientific data and marketing to create meaningful messaging.”<sup>54</sup> Representatives were provided detailed instructions on how to identify and cultivate a “thought leader” who can “[i]nfluence colleagues

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<sup>48</sup> *Id.*

<sup>49</sup> *Id.*

<sup>50</sup> *Id.*

<sup>51</sup> *Id.*

<sup>52</sup> Merck, *Specialty Foundations Participant Self-Study Workbook: Specialty Representative Advocate Development* (May 2001)

<sup>53</sup> *Id.* (emphasis added).

<sup>54</sup> *Id.*

through peer-to-peer relationships” and “is very familiar with the prescribing information for the Merck product(s) and understands and supports the medically/legally approved materials for available for the product(s).”<sup>55</sup>

Merck told its representatives that fees and honoraria for speakers could range from \$250 to \$2,000 per engagement.<sup>56</sup>

The Merck documents indicate that education of physicians was not the only barometer of a successful event. Using the abbreviation of “Rx” for prescribing, one curriculum instructed representatives to tally the “% of attendees whose Rx of program-related Merck products increased.”<sup>57</sup>

### III. COMMUNICATIONS ABOUT VIOXX AND ITS RISKS

Merck’s meticulous approach to marketing to physicians is reflected in its communications to physicians about Vioxx and its risks. Beginning in March 2000, a series of studies and news reports raised serious questions about the safety of Vioxx. The Merck documents reveal that the company gave its highly trained representatives detailed instructions for responding to these developments. These instructions had a common theme: reassure physicians about the safety of Vioxx by providing highly questionable information about cardiovascular risks. At the same time, Merck continued to use an array of incentives and messages to inspire its staff to market Vioxx aggressively to physicians.

#### A. The VIGOR Trial

After a major study showed a five-fold increase in the risk of heart attacks for patients on Vioxx, Merck instructed its field staff to show doctors a pamphlet suggesting that Vioxx was 8 to 11 times safer than other anti-inflammatory drugs. This pamphlet summarized studies that were not appropriate for an analysis of cardiovascular safety.

At issue was a clinical trial known as Vioxx Gastrointestinal Outcomes Research (VIGOR), whose results were announced to the public on March 27, 2000,<sup>58</sup> and published in the *New England Journal of Medicine* on November 23, 2000.<sup>59</sup> The study randomly assigned more than 8,000 patients with rheumatoid arthritis into two groups. One group received 50 mg per day

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<sup>55</sup> *Id.*

<sup>56</sup> Merck, *Business Management, HEL Programs* (undated).

<sup>57</sup> Merck, *Planning, Conducting & Following up Successful HEL Programs* (1999).

<sup>58</sup> *Merck Informs Investigators of Preliminary Results of Gastrointestinal Outcomes Study with VIOXX(R)*, PR Newswire (Mar. 27, 2000).

<sup>59</sup> C. Bombadier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, *New England Journal of Medicine*, 1520–8 (Nov. 23, 2000).

of Vioxx for approximately nine months, while the other received the anti-inflammatory drug naproxen. According to Merck’s press release, the patients receiving Vioxx had fewer gastrointestinal problems, while the patients receiving naproxen suffered fewer heart attacks and strokes.<sup>60</sup> The actual data from the study showed that patients in the VIGOR study on Vioxx were five times more likely to suffer a heart attack than those on naproxen.<sup>61</sup>

Soon after the release of these results, physicians began asking Merck representatives whether Vioxx could cause heart attacks. On April 28, 2000, in a bulletin to “all field personnel with responsibility for Vioxx,” Merck provided a “new resource” “to ensure that you are well prepared to respond to questions about the cardiovascular effects of Vioxx.”<sup>62</sup> The resource was the “Cardiovascular Card.”

The Cardiovascular Card was a tri-fold pamphlet containing data that supported the safety of Vioxx. One panel, featuring the headline “Overall Mortality Rates,” indicated that patients on Vioxx were 11 times less likely to die than patients on standard anti-inflammatory drugs, and 8 times less likely to die from heart attacks and strokes.<sup>63</sup> See Figure 5. Another panel indicated that the rate of heart attack among patients on Vioxx was less than half of the rate of patients receiving placebo and virtually identical to that of patients receiving other anti-inflammatory drugs.<sup>64</sup>

**Figure 5: Selection from the Cardiovascular Card**

<b>Overall mortality and cardiovascular mortality<sup>*1</sup></b>			
<b>Events per 100 Patient-Years</b>			
	<b>VIOXX</b> N=3,595	NSAIDs <sup>†</sup> N=1,565	Placebo N=783
Total mortality	0.1	1.1	0.0
Cardiovascular mortality	0.1	0.8	0.0

<sup>60</sup> Merck took the position that the study’s cardiovascular results showed the cardioprotective effect of naproxen, not the dangers of Vioxx. *Merck Informs Investigators of Preliminary Results of Gastrointestinal Outcomes Study with VIOXX(R)*, PR Newswire (Mar. 27, 2000).

<sup>61</sup> Merck, *Bulletin for Vioxx: New Obstacle Response* (May 1, 2000).

<sup>62</sup> Merck, *Bulletin for Vioxx: NEW RESOURCE: Cardiovascular Card* (Apr. 28, 2000).

<sup>63</sup> Merck, *Cardiovascular System*, 4 (2000).

<sup>64</sup> *Id* at 3.

Merck gave its representatives specific instructions on how to use the Cardiovascular Card. According to these instructions, Merck’s representatives were to refer to the mortality data and “use this page to show physicians that in terms of mortality, which is most important to the physician and their patients, the rate for total mortality and cardiovascular mortality was low.”<sup>65</sup>

The data presented in the Cardiovascular Card appears to have little or no scientific validity. The card did not present actual numbers of events or any statistical tests of significance, which are standard in medical communications. It also did not contain any information from the VIGOR study, the most recent study of cardiovascular safety in rheumatoid arthritis patients.<sup>66</sup>

Instead, the card presented pooled data from clinical trials conducted prior to the drug’s approval in osteoarthritis patients. For several reasons, however, these studies were not appropriate for an overall analysis of cardiovascular safety. For example:

- Vioxx’s pre-approval studies involved few patients taking the doses of Vioxx that were linked to heart problems. According to FDA, fewer than 300 patients in these studies took as much as 50 mg per day of Vioxx for more than 6 months,<sup>67</sup> compared to approximately 4,000 patients in the VIGOR study.<sup>68</sup> As a result, the studies were not nearly as sensitive as VIGOR in detecting a possible problem with the drug.
- The pre-approval studies had been conducted to test the efficacy of the drug to treat pain, not to assess whether the drug caused heart attacks and strokes. None of these early studies had included an expert assessment of whether adverse events were related to the cardiovascular system.<sup>69</sup> Such an “adjudication” process improves the quality of the data and was part of the VIGOR study.
- The pre-approval studies varied widely, involving different doses, different patient populations, and different comparator drugs. In 1999, prior to Vioxx’s approval, FDA had expressed serious concerns about combining these disparate studies in a single safety analysis.<sup>70</sup>

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<sup>65</sup> Merck, *Bulletin for Vioxx: NEW RESOURCE: Cardiovascular Card* (Apr. 28, 2000).

<sup>66</sup> Merck, *Cardiovascular System* (2000).

<sup>67</sup> Food and Drug Administration, *FDA Advisory Committee Briefing Document, NDA 21-042, s007, VIOXX Gastrointestinal Safety*, 19 (Feb. 8, 2001).

<sup>68</sup> *Id.* at 5.

<sup>69</sup> Telephone briefing between Merck and minority staff, Government Reform Committee (Apr. 28, 2005).

<sup>70</sup> In 1999, Merck attempted to combine the pre-approval studies to advance a position on Vioxx’s gastrointestinal safety. FDA made a special presentation to the advisory committee on the problems with combining these different studies. Food and Drug Administration, Arthritis Advisory Committee, *Review of NDA #21-042, Vioxx (Rofecosib) Merck Research Laboratories*, 162–167 (Apr. 20, 1999).

The analyses presented in the Cardiovascular Card were not drawn from a scientific paper.<sup>71</sup> The card's two references included "data on file" at Merck and a brief research abstract from a 1999 meeting of the American College of Rheumatology.<sup>72</sup>

When given the opportunity, FDA scientists have expressed "serious concerns" about using the data summarized on the Cardiovascular Card to address cardiovascular safety.<sup>73</sup> One FDA medical reviewer, in a briefing this week with Committee staff, said that the relevance of Vioxx's pre-approval studies to the drug's cardiovascular safety was "nonexistent" and that it would be "ridiculous" and "scientifically inappropriate" to present mortality comparisons from these trials to physicians.<sup>74</sup>

On May 1, 2000, Merck sent another bulletin to "all field personnel with responsibility for Vioxx."<sup>75</sup> This bulletin instructed the sales force how to respond to a competitor's argument that "Vioxx has an increased incidence of heart attacks compared to Celebrex."<sup>76</sup> This response again involved advice to representatives to respond to physicians by "guiding them through the Cardiovascular Card."<sup>77</sup>

Notwithstanding the results of the VIGOR study, Merck's employees were given new financial incentives to sell Vioxx. In the spring of 2000, Merck launched the "2000 Field

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<sup>71</sup> A pooled analysis of a subset of the studies included in the card was published in the January 15, 2002, issue of the *American Journal of Cardiology*. This analysis did not provide any data on mortality and did not present data on strokes and heart attacks as presented in the Cardiovascular Card. A. Reicin et al., *Comparison of Cardiovascular Thrombotic Events in Patients with Osteoarthritis Treated with Rofecoxib Versus Nonselective Nonsteroidal Anti-Inflammatory Drugs (Ibuprofen, Diclofenac, and Nabumetone)*, *American Journal of Cardiology*, 204–9 (Jan. 15, 2002).

<sup>72</sup> When compared against the abstract, the Cardiovascular Card appears to substantially overstate the amount of data used for the analysis of mortality. According to the abstract, this analysis was based on data from 3,595 patients on Vioxx treated for an average of 5.5 months each. By contrast, the Cardiovascular Card indicates that the mortality analysis was based upon 3,595 "person-years" of data on Vioxx. This would be the equivalent of 3,595 patients treated for an average of 12 months each. Brian Daniels and Beth Seidenberg Rahway, *Cardiovascular Safety Profile of Rofecoxib in Controlled Clinical Trials*, *Arthritis and Rheumatism*, S143 (1999).

<sup>73</sup> Food and Drug Administration, *FDA Advisory Committee Briefing Document, NDA 21-042, s007, VIOXX Gastrointestinal Safety*, 19 (Feb. 8, 2001).

<sup>74</sup> FDA briefing for staff of the Government Reform Committee (May 3, 2005).

<sup>75</sup> Merck, *Bulletin for Vioxx: New Obstacle Response* (May 1, 2000).

<sup>76</sup> *Id.*

<sup>77</sup> *Id.*

Incentive Plan for Vioxx.”<sup>78</sup> This plan promised rewards to the company’s hospital representatives, specialty representatives, and other sales representatives if the Vioxx share of the market for exceeded certain thresholds. As a bulletin to field staff explained:

1. Hit 51% . . . for at least one month by March 2000 and get \$2,000!
2. Hit 55% . . . for at least one month between April and December 2000 and get \$2,000!
3. Hit 61% . . . for at least one month between April and December 2000 and get \$2,000!<sup>79</sup>

To achieve this sales growth, in mid-2000, Merck set a basic strategy for outreach to physicians. The plan was for field representatives to highlight Vioxx’s effectiveness against pain and to transition quickly from any discussion with doctors on safety back to efficacy. As a memo to company vice presidents dated July 28, 2000, stated:

In order to win the on-going . . . battle, many of you agree our sales force needs to STOP defending Vioxx against the outrageous claims from our competitors, and START offensively selling the core benefit of this product . . . EFFICACY.<sup>80</sup>

#### **B. The FDA Advisory Committee Meeting**

Attention to the cardiovascular risks of Vioxx surged in February 2001 as the result of a meeting of the FDA Arthritis Advisory Committee. After FDA scientists raised serious concerns about the drug’s safety, the Committee voted that doctors should be informed about the data from the VIGOR study. The next day, however, Merck instructed its field representatives not to discuss the VIGOR results with doctors and instead reassure physicians using the Cardiovascular Card.

In advance of the advisory committee meeting, FDA scientists provided the Committee with an analysis of all studies on Vioxx conducted to date.<sup>81</sup> FDA’s assessment covered:

- The VIGOR study, which found a substantial and statistically significant increase in all serious thrombotic events, including heart attack and stroke, in patients on Vioxx compared to patients on naproxen;<sup>82</sup>

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<sup>78</sup> Merck, *Bulletin for Vioxx: 2000 Field Incentive Plan for Vioxx* (Apr. 5, 2000).

<sup>79</sup> *Id.*

<sup>80</sup> Merck, *Memo re: Offensive Positioning for Vioxx* (July 28, 2000).

<sup>81</sup> Food and Drug Administration, *FDA Advisory Committee Briefing Document, NDA 21-042, s007, VIOXX Gastrointestinal Safety*, 19 (Feb. 8, 2001).

<sup>82</sup> *Id.* at 9–12.

- Another study, called the Advantage study, which showed a trend toward excess heart attacks in osteoarthritis patients in the Vioxx group, compared to naproxen,<sup>83</sup> and
- Two new studies, 085 and 090, which, according to FDA, appeared to “follow the pattern observed in the VIGOR study.” These studies were conducted in patients with osteoarthritis.<sup>84</sup>

FDA also addressed whether Vioxx’s pre-approval studies, which were the basis of the Cardiovascular Card, could be used to assess the drug’s cardiovascular safety. The agency informed the committee that the studies should not be used for a safety analysis. Regarding the pre-approval study 058, the FDA reviewer wrote:

Because of the small size and short duration, this study is inadequate to detect differences in clinically relevant adverse events between rofecoxib [Vioxx] and nabumetone [another anti-inflammatory drug].<sup>85</sup>

Regarding study 069, which contained data on a set of other pre-approval studies, the reviewer stated:

The Division has serious concerns with a combined analysis of studies of different length and dosing regimens. The database overall included short term, low doses of rofecoxib [Vioxx]. . . . None of the studies were powered to detect differences in serious CV [cardiovascular] thrombotic events compared to the active comparator.<sup>86</sup>

The Arthritis Advisory Committee heard from FDA, the public, and Merck.<sup>87</sup> The Committee then concluded that clinicians should be informed that VIGOR study showed “an excess of cardiovascular events in comparison to naproxen.”<sup>88</sup>

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<sup>83</sup> *Id.* at 18.

<sup>84</sup> *Id.* at 17.

<sup>85</sup> *Id.* at 19.

<sup>86</sup> *Id.*

<sup>87</sup> At the meeting, Merck presented a large pooled analysis of all Vioxx trials. In response, FDA told the advisory committee that combining so many different studies to assess safety was fundamentally flawed. Bonnie Goldmann, Regulatory Affairs, Merck Research Laboratories, *FDA Arthritis Advisory Committee* (Feb. 8, 2001); Quan Li, *Advisory Committee Presentation on Vioxx: Discussion on the Metaanalysis for Cardiovascular Risk Assessment* (Feb. 8, 2001).

<sup>88</sup> Food and Drug Administration, *Transcript of Meeting of Arthritis Advisory Committee, NDA # 21-042/s007, Vioxx (Rofecoxib, Merck)*, 206 (Feb. 8, 2001).

The next day, Merck sent a bulletin to “all field personnel with responsibility for Vioxx.”<sup>89</sup> The bulletin instructed the sales force to “stay focused on the EFFICACY messages for VIOXX.”<sup>90</sup> Contrary to the Committee’s recommendation, the bulletin advised:

DO NOT INITIATE DISCUSSIONS ON THE FDA ARTHRITIS ADVISORY COMMITTEE ... OR THE RESULTS OF THE ...VIGOR STUDY.<sup>91</sup>

To respond to doctors who asked about these topics, Merck instructed its field representatives to take three steps.

First, Merck told representatives to say that “because the study is not in the label, I cannot discuss the study with you.”<sup>92</sup> This position did not accurately reflect FDA regulations. Under the law, pharmaceutical representatives are permitted to discuss evidence of safety concerns with doctors, even if such data are not on the drug’s label.<sup>93</sup>

Second, Merck told the representatives to advise physicians to submit written questions to the company’s medical services department. Responses to these questions described the same highly questionable data used in the Cardiovascular Card data before discussing VIGOR and other studies. For example, one response to a clinician contained the same mortality table used in the Cardiovascular Card, but without the column for “placebo.” The text stated, “Both the overall mortality . . . and the cardiovascular mortality was lower in the rofecoxib [Vioxx] group compared to the NSAID group.”<sup>94</sup>

Third, Merck told representatives to refer to the Cardiovascular Card.<sup>95</sup> Staff were apparently instructed not to leave this pamphlet with physicians.<sup>96</sup>

FDA’s advisory committee meeting did not slow Merck’s marketing of Vioxx. Early in 2001, Merck launched “Project A&A XXceleration” to reach sales goals through “revised

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<sup>89</sup> Merck, *Bulletin for Vioxx: FDA Arthritis Advisory Committee Meeting for Vioxx* (Feb. 9, 2001).

<sup>90</sup> *Id.*

<sup>91</sup> *Id.*

<sup>92</sup> Merck, *Bulletin for Vioxx: FDA Arthritis Advisory Committee Meeting for Vioxx* (Feb. 9, 2001).

<sup>93</sup> 21 CFR 202.1

<sup>94</sup> Letter from Jeffrey M. Melin, Associate Director, Medical Services to Dr. Joseph Torg (Mar. 16, 2001).

<sup>95</sup> Merck, *Bulletin for Vioxx: FDA Arthritis Advisory Committee Meeting for Vioxx* (Feb. 9, 2001).

<sup>96</sup> It was a “non leave” sales aid. *Id.*

targeting, messaging and advocate development.”<sup>97</sup> “A&A” refers to arthritis and analgesia, two clinical indications for Vioxx. The slogan for Project A&A XXceleration was apparently “In It to Win It.”<sup>98</sup>

As part of this effort, in an April 2001 bulletin for office-based field staff, Merck instructed that each salesperson make a list of his or her “top 50” physicians who were considered “high volume targets.”<sup>99</sup>

On April 27, 2001, Merck executive Jo Jerman left a voice mail for field staff involved in Project A&A XXceleration. She stated:

The most recent performance numbers show a continued trend upward ... the share of VIOXX in the A&A market is up to 17.2% — that’s an all time high —and the share of VIOXX in the Coxib market 51.2% — another all-time high. Woo doggie! That is exciting.<sup>100</sup>

She concluded:

The only thing left is to put “Project A&A XXceleration” into overdrive ... the time is now and I wouldn’t want anyone on the task but all of you. Last, but certainly not least, you’ve got some extra dollars to shoot for as well. As you recall from our incentive program, if you hit those 2–4 share point increases, you’ll be rewarded handsomely . . . . Go get em guys, Good luck and Great selling!<sup>101</sup>

### **C. The New York Times Article**

On May 22, 2001, a long article on the front page of the business section of the *New York Times* raised questions about the cardiovascular safety of Vioxx. Merck responded by instructing representatives to read favorable data on the Cardiovascular Card directly to physicians.

The *New York Times* article described a pharmaceutical industry analyst who “was warning his clients, many of them institutional investors who hold Merck shares, that they should

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<sup>97</sup> Merck, *Bulletin for Vioxx: ACTION REQUIRED—“Project A&A Accleration”*: Top 50 Targeting (Apr. 20, 2001).

<sup>98</sup> Merck, *MVX for Vioxx: Jo Jerman, Audience—Field Sales, April 27, 2001, Topic: Project A&A XXceleration, Length—approx 1 min 30 Sec* (Apr. 27, 2001).

<sup>99</sup> Merck, *Bulletin for Vioxx: ACTION REQUIRED—“Project A&A Accleration”*: Top 50 Targeting (Apr. 20, 2001).

<sup>100</sup> Merck, *MVX for Vioxx: Jo Jerman, Audience—Field Sales, April 27, 2001, Topic: Project A&A XXceleration, Length—approx 1 min 30 Sec* (Apr. 27, 2001).

<sup>101</sup> *Id.*

watch the issue carefully since it could hurt the company's stock price." The article also quoted FDA Arthritis Advisory Committee member Dr. M. Michael Wolfe, who stated, "There must be a warning . . . . The marketing of these drugs is unbelievable . . . . I'm sure there are many people out there who are taking these drugs that should not be."<sup>102</sup>

In response, Merck quickly issued a press release entitled "Merck Confirms Favorable Cardiovascular Safety of Vioxx."<sup>103</sup> Inside FDA, scientists rejected this conclusion. In a warning letter to the company sent several months later, FDA would cite the title of Merck's press release as "simply incomprehensible" in the face of data from the VIGOR study.<sup>104</sup>

A Merck bulletin to its field representatives also emphasized the drug's safety. The bulletin again advised:

DO NOT INITIATE DISCUSSIONS ON THE RESULTS OF THE ... VIGOR STUDY, OR ANY OF THE RECENT ARTICLES IN THE PRESS ON VIOXX.<sup>105</sup>

In the case that a physician had further questions, Merck instructed its representatives to display the Cardiovascular Card. The bulletin told field staff to highlight data on the card suggesting that Vioxx might be much safer than other "NSAIDS," non-steroidal anti-inflammatory drugs.<sup>106</sup> Specifically, Merck advised representatives to state:

Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was Vioxx .1 vs. NSAIDs .8 vs. Placebo 0.<sup>107</sup>

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<sup>102</sup> *Doubts Are Raised on the Safety of Two Popular Arthritis Drugs*, New York Times (May 22, 2001).

<sup>103</sup> Merck, *Merck Confirms Favorable Cardiovascular Safety of Vioxx* (May 22, 2001).

<sup>104</sup> This warning letter contained other examples of inappropriate promotions of Vioxx. These were educational events in 2000 in which a Merck consultant provided false data or made extremely inappropriate comparisons between Vioxx and other products. In response, Merck stated that the events violated company policy and had stopped using the speaker in question. At the request of FDA, Merck also sent letters to physicians who attended the educational events. Letter from Thomas W. Abrams, Director, Division of Marketing, Advertising and Communications, Food and Drug Administration, to Raymond V. Gilmartin, President and CEO, Merck & Co, Inc. (Sept. 17, 2001); Letter from Louis M. Sherwood, Senior Vice President, U.S. Medical & Scientific Affairs, Merck, to Health Care Provider (Nov. 2001).

<sup>105</sup> Merck, *Bulletin for Vioxx: Action Required: Response to New York Times Article* (May 23, 2001).

<sup>106</sup> *Id.*

<sup>107</sup> *Id.*

#### D. JAMA Study

On August 22, 2001, a study published in the *Journal of the American Medical Association (JAMA)* raised serious questions about the safety of Vioxx and other drugs in its class. In an alert to field representatives about this study, Merck urged them to express confidence in Vioxx's cardiovascular safety and use the Cardiovascular Card.

The *JAMA* paper reviewed new data from VIGOR and other recent studies on the safety of Vioxx and Celebrex, a similar drug.<sup>108</sup> Authors Dr. Debobrate Mukherjee, Dr. Steven E. Nissen, and Dr. Eric J. Topol from the Cleveland Clinic concluded that there was evidence of a “potential increase in cardiovascular event rates for the presently available COX-2 inhibitors.”<sup>109</sup> Until additional studies of safety are conducted, they wrote, “we urge caution in prescribing these agents to patients at risk for cardiovascular morbidity.”<sup>110</sup>

One day prior to the *JAMA* paper's release, Merck executive Jo Jerman left a confident and reassuring voice mail for the company's field representatives. She stated:

#1. Stay focused. Stay focused with your efficacy and GI risk awareness messages and stay focused with your confidence in cardiovascular safety and overall safety of VIOXX.<sup>111</sup>

Ms. Jerman also instructed representatives that “if asked about CV effects, use your CV card.”<sup>112</sup> She continued: “As your piece shows, CV events and cardiovascular mortality rates between Vioxx and NSAIDS ... were similar in [osteoarthritis] studies.”<sup>113</sup> Ms. Jerman then reminded Merck's field representatives that additional information from the medical services department could be faxed to physicians upon request.<sup>114</sup>

The *JAMA* paper did not lead Merck to moderate its approach to selling Vioxx. Instead, in the fall of 2001, Merck launched Project Offense, a major new marketing campaign with the

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<sup>108</sup> D. Mukherjee, S. Nissen, E. Topol, *Risk of Cardiovascular Events Associated with Selective Cox-2 Inhibitors*, *Journal of the American Medical Association*, 954–9 (Aug. 22–29, 2001).

<sup>109</sup> *Id.*

<sup>110</sup> *Id.*

<sup>111</sup> Merck, *MVX for Vioxx, Field Sales—USHH, Jo Jerman, August 21, 2001, “JAMA article” FINAL (approx 4 minutes)*, 3 (Aug. 21, 2001).

<sup>112</sup> *Id.*

<sup>113</sup> *Id.*

<sup>114</sup> *Id.*

goal of increasing Vioxx's share of the market.<sup>115</sup> The central message of Project Offense was efficacy. The company instructed its sales representatives to emphasize that Vioxx demonstrated a potential advantage over narcotics for pain management.

As part of Project Offense, Merck instructed field representatives to deliver the efficacy message multiple times to top prescribers (those physicians who had the highest rates of prescribing Vioxx to their patients). The representatives were also expected to "quickly and effectively address all physician obstacles and return to the core messages for VIOXX."<sup>116</sup> Merck used the term "obstacles" to refer to concerns physicians might have about prescribing Vioxx.

Project Offense included a decision tree to help address the cardiovascular safety concerns of physicians. Known as the "CV Obstacle Response," this decision tree began by advising field representatives to tell doctors about the differences between Vioxx and aspirin.<sup>117</sup>

Merck then advised its field representatives to "REVIEW ENTIRE CV CARD" with doctors, including:

- CV thromboembolic Adverse Events per 100 patient years
- Specific CV events
- Overall Mortality
- CV Mortality<sup>118</sup>

The "CV Obstacle Response" concluded:

Doctor, I hope this data has addressed your concern. Let me show you some new efficacy data for VIOXX.<sup>119</sup>

#### **E. Changes to the Vioxx Label**

Nearly two years after Merck filed a request for label changes for Vioxx based on the results of the VIGOR study, FDA approved a new label that discussed the cardiovascular risks of the drug. The extended delay resulted, in part, from FDA's need to convene an advisory committee meeting and conduct extra analyses. It also was due to a series of disputes between the agency and the company. Under the Food, Drug and Cosmetic Act, FDA and manufacturers must agree on label changes. For approximately six months, Merck resisted a variety of FDA's

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<sup>115</sup> Merck, *Project OFFENSE MEETING AGENDA & CONTENT: Representative Meetings* (2001).

<sup>116</sup> *Id.*

<sup>117</sup> *Id.*

<sup>118</sup> *Id.*

<sup>119</sup> *Id.*

proposals, leading to an extended series of conference calls to negotiate differences. Throughout this period, Merck continued to use the Cardiovascular Card with physicians. Eventually, it appears that FDA officials conceded on several key points of dispute.

FDA initially requested that the label warn physicians that Vioxx could cause heart attacks and other cardiovascular problems. FDA proposed that the warning state:

VIOXX should be used with caution in patients at risk of developing cardiovascular thrombotic events such as those with a history of myocardial infarction and angina and in patients with pre-existent hypertension and congestive heart failure.

The risk of developing myocardial infarction in the VIGOR study was five fold higher in patients treated with VIOXX 50 mg (0.5%) as compared to patients treated with naproxen (0.1%). . . . This finding was consistent in a smaller and shorter study using VIOXX 25 mg that allowed the use of low dose ASA [aspirin]. Prospective, well powered, long-term studies required to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators other than naproxen have not been performed.<sup>120</sup>

This warning was unacceptable to Merck, which sought to move information on the VIGOR study to the “precautions” section.<sup>121</sup>

Merck sought to add additional data to the label from other studies, including results from ongoing studies in Alzheimer’s Disease.<sup>122</sup> FDA initially advised against including these studies, saying that the studies should be completed and their findings incorporated in the label later.<sup>123</sup>

On February 15, 2002, FDA proposed to Merck that the label include a special graphic called a Kaplan-Meier curve to show a worsening of cardiovascular risks on Vioxx for those with the longest exposure to the drug.<sup>124</sup> During a teleconference, FDA officials stated that the “best way to display the data is the Kaplan Meier curve.”<sup>125</sup> FDA’s minutes of the call add, “Note: The time devoted to how to best display cardiovascular safety from VIGOR reflects how important the Agency considers the topic of clear labeling of safety information.”<sup>126</sup> Merck objected to the idea.<sup>127</sup>

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<sup>120</sup> Merck, *FDA Text of 15 Oct 2001 with Merck Proposals Shown with Revision Marks* (2001).

<sup>121</sup> *Id.*

<sup>122</sup> Food and Drug Administration, *Telecon Minutes* (Jan. 30, 2002).

<sup>123</sup> *Id.*

<sup>124</sup> Food and Drug Administration, *Telecon Minutes* (Mar. 7, 2002).

<sup>125</sup> *Id.*

<sup>126</sup> *Id.*

<sup>127</sup> *Id.*

By the end of the negotiation, FDA gave ground on several key issues. Two Alzheimer's studies, which showed no increase in cardiovascular events, were noted in the label. The Kaplan-Meier curve was not included. The cardiovascular risk was listed not as a "warning," but as a "precaution." And perhaps most important to Merck, the label included the statement that "the significance of the cardiovascular findings of these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown."

But Merck did not get everything it wanted in the label. The company had sought to include in the label data from Vioxx's pre-approval studies — the same studies summarized in the Cardiovascular Card that the company's representatives had been showing to physicians for two years.<sup>128</sup> FDA rejected Merck's proposal. According to the agency, the analysis of pre-approval data was "not adequately informative to warrant inclusion in the label" because the analysis included "trials of different design, size, and duration, using different doses of VIOXX and different comparators."<sup>129</sup>

After the label change, Merck altered its instructions to field representatives regarding cardiovascular risk. The new instructions still prohibited representatives from initiating discussion on any new cardiovascular data. But the instructions now drew heavily from the language in the label that emphasized uncertainty about the cardiovascular risk of the drug.

For example, on September 17, 2003, Merck sent a bulletin to its sales representatives about a pending abstract to be presented at a meeting of the American College of Rheumatology. The abstract, which was based on epidemiological research funded by Merck, reported a higher risk of heart attack in patients on Vioxx compared to those on its competitor Celebrex or placebo.<sup>130</sup> Merck instructed its representatives:

DO NOT INITIATE DISCUSSIONS ON ANY OF THE UPCOMING ABSTRACTS ON VIOXX THAT WILL BE PRESENTED AT THIS YEAR'S AMERICAN COLLEGE OF RHEUMATOLOGY MEETING.<sup>131</sup>

The bulletin contained an "obstacle response" to be used in case a physician asked a Merck representative about the study. The response instructed representatives to review selected portions of the label and then say, "As stated here in the label, the significance of the cardiovascular findings ... is unknown."<sup>132</sup>

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<sup>128</sup> Food and Drug Administration, *Telecon Minutes* (Feb. 8, 2002).

<sup>129</sup> *Id.*

<sup>130</sup> Merck, *Bulletin for VIOXX: Upcoming Abstracts for VIOXX at the 2003 American College of Rheumatology Meeting and Obstacle Response for Observational Analysis* by Solomon, et. al. (Sept. 17, 2003).

<sup>131</sup> *Id.*

<sup>132</sup> *Id.*

Similar instructions were given to representatives in response to other research showing an elevated risk of cardiovascular complications with Vioxx.<sup>133</sup>

Meanwhile Merck's promotional efforts continued. In 2003, Merck launched "Project Power Play" with the objectives to "gain or extend coxib leadership," "play offense on efficacy," and "stay on strategy."<sup>134</sup>

#### IV. CONCLUSION

A review of over 20,000 pages of Merck documents suggests that the company used its sales force of thousands to counter growing evidence of concern over the safety of Vioxx. These efforts involved providing highly questionable information to physicians and pursuing aggressive marketing strategies. Merck's promotional activities appear to help explain robust sales of Vioxx despite mounting evidence of risk.

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<sup>133</sup> Merck, *Bulletin for Vioxx: Action Required: Observational Analysis by Graham et al.* (Aug. 24, 2004).

<sup>134</sup> Merck, *Bulletin for VIOXX: Project Power Play Teleconferences* (Apr. 4, 2003).